Azeotropic Isopropyl Alcohol

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Expert Committee	Simple Excipients Expert Committee

In accordance with the Rules and Procedures of the Council of Experts, the Simple Excipients Expert Committee has revised the Azeotropic Isopropyl Alcohol monograph. The purpose of the revision is to strengthen the *Identification (ID)* section of the monograph by including the *Limit of Methanol* test as an additional *ID* test.

To address the serious hazards associated with the use of methanol-containing azeotropic isopropyl alcohol, the Simple Excipients Expert Committee (SE) has revised the Azeotropic Isopropyl Alcohol monograph. These revisions are consistent with a letter (Feb. 25, 2021) from, and a recent FDA Guidance (January 2021) issued by the U.S. Food and Drug Administration (FDA). USP previously revised the *USP* Alcohol and *USP* Dehydrated Alcohol monographs by including an Identification C test for "*Limit of Methanol*." Additional information about that topic can be found in the Frequently Asked Questions for Alcohol and Dehydrated Alcohol.

As mentioned in the *Notice of Intent to Revise* posted on Apr. 30, 2021, the purpose of these revisions is to strengthen the *ID* section of the monograph by including the test for *Limit of Methanol* as an additional *ID* test. The new *Limit of Methanol* test utilizes a gas-chromatography (GC) method similar to the *Volatile Impurities* test in the *USP* Azeotropic Isopropyl Alcohol monograph. The limit for methanol (200 µL/L) is the same as that in the *USP* Alcohol monograph, consistent with what is recommended in the FDA Guidance (January 2021). The *Volatile Impurities* GC method is also updated by including the methanol as a specified impurity. Additionally, external reference standards are used for quantitative analysis of each individual impurity.

The changes to the current *USP* Azeotropic Isopropyl Alcohol monograph include:

1. *Identification B.* A new *Limit of Methanol* test is added to the *Identification* section. The test is referring to the *Volatile Impurities* test in the same monograph with a limit for methanol (200 µL/L).

   A note was also included within *Identification B* to emphasize that compliance of identity is determined by meeting the requirements for all identification tests in the monograph as shown below:

   [Note—This test must be performed to be in compliance with USP, in addition to *Identification A* above.]

2. *Volatile Impurities.*
   - Updated the GC method to include the new impurity: Methanol.
   - System suitability solution is updated to include 200 µL/L of methanol and 1000 µL/L of ethyl acetate in USP 2-Propanol System Suitability RS.
   - Clarified that Sample solution is the Azeotropic Isopropyl Alcohol substance under the test.
   - Standard solution A and Standard solution B are added for quantitative analysis of each known and unspecified impurity.
   - The GC conditions are aligned with that in the *USP* Isopropyl Alcohol monograph, including Detector, Flow rate, Split ratio, etc. The 2 min holding time at 45° is deleted. The hold time at final temperature of 100° is extended from 1 min to 5 min to elute late-eluting unknown impurities in some Azeotropic Isopropyl Alcohol samples. As such, the run time is 26 min.
   - Under *System Suitability*,
     - *Table 2* is created to list the relative retention time (RRT) of each impurity, respectively. The RRTs for impurities are also adjusted according to the method

validation results. Please note the RRTs may vary a little bit depending on the instrument and column used.
    - A note is added under *Table 2* to clarify that ethyl acetate is not considered as a known impurity but used as a reference standard to calculate unspecified impurities.
    - For *Suitability requirements*, the number of replicate injections is specified for *Relative standard deviation*. Methanol and ethyl acetate are added to the *Signal-to-noise ratio requirements.*
- Individual impurities are quantitatively determined against their respective reference standards with known concentrations. Ethyl acetate is used as a reference standard for calculation of unspecified impurities.
- The area normalization procedure (% of total detected area) for impurity analysis is deleted. The calculations for methanol, individual known impurities, and individual unspecified impurities are added.
- *Table 3* is created to include the acceptance criteria for methanol (NMT 0.02%, corresponding to 200 µL/L). The limit of NMT 0.1% for individual known impurities (ethyl ether, acetone, diisopropyl ether, 1-propanol, and 2-butanol), and any unspecified impurity is added. The limit for total impurities (NMT 1.0%) is also specified.

As a note to stakeholders, USP Reference Standards (RS) are qualified and suitable for use in the *Limit of Methanol* and *Volatile Impurities* tests, including USP 2-Propanol System Suitability RS (Cat# 1570439), USP Methyl Alcohol RS (Cat# 1424109), USP Acetone RS (Cat# 1006801), USP 1-Propanol RS (Cat# 1570406), and USP 2-Butanol RS (Cat# 1081829). In addition, USP Ethyl Acetate RS (Cat# 1265402) is qualified and suitable for use as an RS for calculations of unspecified impurities.

The Azeotropic Isopropyl Alcohol Revision Bulletin will supersede the currently official monograph and become official on Feb. 1, 2022. USP encourages early adoption by stakeholders as outlined in the *USP General Notices 3.10. Applicability of Standards*.

A similar Revision Bulletin will also be posted for the *USP* Isopropyl Alcohol monograph.

Should you have any questions, please contact Jenny Liu, Principal Scientist (240-221-2072 or jyl@usp.org).

Revision Bulletin
Official: February 1, 2022

Azeotropic Isopropyl Alcohol

To view the Notice from the Expert Committee that posted in conjunction with this accelerated revision, please click https://www.uspnf.com/rb-azeotropic-ipa-20210730.

DEFINITION

Azeotropic Isopropyl Alcohol contains NLT 91.0% and NMT 93.0% of isopropyl alcohol, by volume, the remainder consisting of water.

IDENTIFICATION

● **A. Infrared Absorption:** The IR absorption spectrum of a thin film of it exhibits a strong broad band at 3.0 µm; a strong region of absorption between 3.35 and 3.5 µm, with its highest peak at 3.36 µm, and others at 3.41 and 3.47 µm; many weak peaks between 3.6 and 6.0 µm, among the most noticeable being those at 3.68, 3.77, 3.97, 4.17, and 5.26 µm; a broad band at 6.2 µm; a strong region of absorption between 6.7 and 7.8 µm, the most prominent features being the peaks at 6.80, 7.09, 7.25 (the highest), 7.46, and 7.63 µm; a strong region of absorption between 8.5 and 9.2 µm, peaking at 8.6, 8.85, and 9.0 µm; and strong peaks at 10.5 and 12.3 µm.

Add the following:

▲● **B. Limit of Methanol**

[Note—This test must be performed to be in compliance with USP, in addition to *Identification A* above.]

System suitability solution, Sample solution, Standard solution A, Chromatographic system, and **System suitability:** Proceed as directed in the *Volatile Impurities* test.

Analysis: Proceed as directed in the *Volatile Impurities* test, *Methanol calculation*.

Acceptance criteria: Meets the requirements in *Table 3* for methanol ▲ (RB 1-Feb-2022)

IMPURITIES

● **Limit of Nonvolatile Residue**

Sample: 50 mL

Analysis: Evaporate the *Sample* in a tared porcelain dish on a steam bath to dryness, and heat at 105° for 1 h.

Acceptance criteria: The weight of the residue does not exceed 2.5 mg (0.005%).

Change to read:

● **Volatile Impurities**

System suitability solution: ▲200 µL/L of methanol and 1000 µL/L of ethyl acetate in ▲ (RB 1-Feb-2022) USP 2-Propanol System Suitability RS

Sample solution: Azeotropic Isopropyl Alcohol ▲(Substance under test)

Standard solution A: 200 µL/L of methanol in *Sample solution*

[Note—To be performed as a part of *Identification B*.]

Standard solution B: 1000 µL/L each of acetone, diisopropyl ether, ethyl ether, 1-propanol, 2-butanol, and ethyl acetate in *Sample solution* ▲ (RB 1-Feb-2022)

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: GC

Detector: ▲Flame ionization▲ (RB 1-Feb-2022)

Column: 0.25-mm × 60-m, coated with a 1.4-µm film of phase G43

Temperature

Injector: 150°

Detector: 200°

Column: See *Table 1*.

Table 1

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
35	▲—▲ (RB 1-Feb-2022)	35	5
35	1	45	▲—▲ (RB 1-Feb-2022)
45	10	100	▲5▲ (RB 1-Feb-2022)

Carrier gas: Helium

▲**Flow rate:** 2.3 mL/min▲ (RB 1-Feb-2022)

Injection ▲volume:▲ (RB 1-Feb-2022) 1 µL

▲**Injection type:** Split injection; split ratio is about 50:1. [NOTE—A 4-mm straight liner is suitable.]▲ (RB 1-FEB-2022)

Run time: ▲26▲ (RB 1-Feb-2022) min

System suitability

Sample: *System suitability solution*

▲[NOTE—See *Table 2*.]

Table 2

Name	Relative Retention Time
Methanol	0.5
Ethyl ether	0.8
Acetone	0.9
Isopropyl alcohol	1.0
Diisopropyl ether	1.3

Name	Relative Retention Time
n-Propyl alcohol (1-propanol)	1.4
Ethyl acetate[a]	1.6
2-Butanol	1.7▲ (RB 1-Feb-2022)

[a] Ethyl acetate Reference Standard is not a known impurity. It is used for the calculation of unspecified impurities only.

Suitability requirements

Resolution: NLT 1.5 between acetone and isopropyl alcohol

Signal-to-noise ratio: NLT 10 for any of the following peaks: ▲methanol,▲ (RB 1-Feb-2022) ethyl ether, acetone, isopropyl alcohol, diisopropyl ether, 1-propanol, 2-butanol, ▲and ethyl acetate.▲ (RB 1-Feb-2022)

Tailing factor: NMT 2.0 for the isopropyl alcohol peak

Relative standard deviation: NMT 2.0% for the isopropyl alcohol peak ▲of 6 replicate injections of *System suitability solution*▲ (RB 1-Feb-2022)

Analysis

Samples: *Sample solution*, ▲*Standard solution A*, and *Standard solution B*

Methanol calculation

[NOTE—To be performed as a part of *Identification B*.]

$$\text{Result (\% v/v)} = \{[M_U/(M_S - M_U)] \times C_M\}/10{,}000$$

M_U = peak area of methanol in the *Sample solution*

M_S = peak area of methanol in *Standard solution A*

C_M = concentration of spiked methanol in *Standard solution A* (µL/L)

Individual known impurity (ethyl ether, acetone, diisopropyl ether, 1-propanol, 2-butanol) calculation

$$\text{Result (\% v/v)} = \{[K_U/(K_S - K_U)] \times C_K\}/10{,}000$$

K_U = peak area of individual known impurity in the *Sample solution*

K_S = peak area of individual known impurity in *Standard solution B*

C_K = concentration of spiked individual known impurity in *Standard solution B* (µL/L)

Individual unspecified impurity calculation

$$\text{Result (\% v/v)} = [(r_U/r_S) \times C_S]/10{,}000$$

r_U = peak area of each unspecified impurity in the *Sample solution*

r_S = peak area of ethyl acetate in *Standard solution B*

C_S = concentration of ethyl acetate in *Standard solution B* (µL/L)▲ (RB 1-Feb-2022)

Acceptance criteria: ▲See *Table 3*.

Table 3

Impurity	Percentage (% v/v)
Methanol[a]	NMT 0.02[a]
Each other individual known impurity (ethyl ether, acetone, diisopropyl ether, 1-propanol, 2-butanol)	NMT 0.1
Individual unspecified impurity	NMT 0.1
Total impurities	NMT 1.0▲ (RB 1-Feb-2022)

[a] To be performed as a part of *Identification B*.

SPECIFIC TESTS

- **Specific Gravity ⟨841⟩:** 0.815–0.810, indicating 91.0%–93.0% of isopropyl alcohol (C_3H_8O) by volume
- **Refractive Index ⟨831⟩:** 1.376–1.378 at 20°
- **Acidity**

  Sample: 50 mL

  Analysis: Place the *Sample* in a suitable flask, and add 100 mL of carbon dioxide-free water. Add 2 drops of phenolphthalein TS, and titrate with 0.020 N sodium hydroxide to a pink color that persists for 30 s.

  Acceptance criteria: NMT 0.70 mL of 0.020 N sodium hydroxide is required for neutralization.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers, remote from heat.
- **USP Reference Standards ⟨11⟩**

  USP 2-Propanol System Suitability RS

  It is a mixture of the following: ethyl ether (0.1%), acetone (0.1%), diisopropyl ether (0.1%), 1-propanol (0.1%), 2-butanol (0.1%), and isopropyl alcohol (99.5%).

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